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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/862,855	05/21/2001	Hong Cai	S-94,652	8369

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EXAMINER
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STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
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1637

MAIL DATE	DELIVERY MODE
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04/09/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary**

Application No.

09/862,855

Applicant(s)

CAI ET AL.

Examiner

Teresa E. Strzelecka

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 16 October 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 5, 17 and 20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4, 8-16, 18, 19 and 21 is/are rejected.
- 7) ☒ Claim(s) 6, 7 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |                                                                                      |                                                                   |
|--------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date. _____                                                         | 6) <input type="checkbox"/> Other: _____                          |

### DETAILED ACTION

1. This office action is in response to an amendment filed June 27, 2007. Claims 1-21 were previously pending, with claims 5, 17 and 20 withdrawn from consideration. Applicants cancelled claims 1, 4 and 21 and amended claims 2, 3, 8, 9 and 15. Claims 2, 3 and 5-20 are pending, with claims 5 and 17 withdrawn from consideration.

2. Applicants' amendments overcame the rejections presented in the previous office action. This office action contains new grounds for rejection necessitated by amendments.

3. Applicants' arguments are moot in view of new grounds for rejection.

#### *Claim Rejections - 35 USC § 103*

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 2, 3 and 8-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kostrikis et al. (Science, vol. 279, pp. 1228-1229, 1998; cited in the IDS and in the previous office action) and Ruano et al. (PNAS USA, vol. 87, pp. 6296-6300, 1990; cited in the IDS).

A) Regarding claim 2, Kostrikis et al. teach a method of haplotyping comprising:

labeling at least two target sites on a segment of unamplified DNA or RNA with separate distinguishable luminescent hybridization probes, where the targets are selected genetic markers (Kostrikis et al. teach forming at least two luminescent pairs of probes for at least two polymorphic sites, where each pair contains a probe hybridizing to a wild-type polymorphism and a probe hybridizing to a mutant polymorphism, and where each probe is labeled with a different fluorescent

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label (Fig. 1; page 1228, second and third paragraph). They teach labeling of unamplified DNA or RNA segments directly with molecular beacons (page 1229, last paragraph).);

illuminating each labeled DNA or RNA segment with light beams (Kostrikis et al. teach illuminating the tubes with amplification reactions using light beams (page 1228, last paragraph; page 1229, first paragraph).); and

detecting the presence or absence of each luminescent hybridization probe on each DNA segment to determine the haplotype of each DNA or RNA segment (Kostrikis et al. teach analyzing the set of outputs to determine the haplotype of the chromosome pair (Fig. 1, 2; page 1229, second paragraph).).

Regarding claim 3, Kostrikis et al. teach genotyping other alleles (page 1229, third paragraph).

Regarding claim 8, Kostrikis et al. teach detection of deletions (page 1228, third paragraph) and point mutations (page 1229, third paragraph).

Regarding claims 9 and 12, Kostrikis et al. teach detection of the probes based on their emission spectral distribution (page 1228, second paragraph).

Regarding claims 10 and 13, Kostrikis et al. teach molecular beacons (page 1228, second paragraph).

Regarding claims 11, 14, 16 and 19, Kostrikis et al. teach DNA probes (page 1229, reference 12).

Regarding claims 15 and 18, Kostrikis et al. teach single probes specific for each target (page 1228, second paragraph; page 1229, reference 12).

B) Kostrikis et al. do not teach diluting the samples of labeled DNA segments, but teach that direct detection of the target nucleic acids could be achieved using small sample volumes (page 1229, last paragraph).

C) Ruano et al. teach haplotyping by making dilutions of target nucleic acid sequences to the level of about one molecule per sample (page 6296, last paragraph; page 6297, first paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the dilution method of Ruano et al. in the haplotyping method of Kostrikis et al. The motivation to do so, provided by Ruano et al., would have been that the dilution method resolved ambiguities in polymorphism arrangement and allowed direct determination of a haplotype (page 6296, last paragraph; page 6297, first paragraph). As stated by Ruano et al. (page 6300, last paragraph):

“Genome analysis utilizing SMD has particular relevance to evolution and medicine.

Evolutionary studies of wild animal populations or anthropological isolates often depend on samples lacking organized families; SMD allows direct haplotyping of such field samples.

Haplotypes have far more information content than classical protein polymorphisms and allow the reconstruction of the evolutionary history of a locus. In other biological contexts that require individual identification or knowledge of familial relationships, haplotypes serve as informative genetic markers. In medical applications, the increased information content of haplotypes makes them attractive as potential markers for improving the diagnosis of any linked disease genes or in epidemiological population screens for detecting specific haplotypes known to be associated with disease mutations (25, 26). Similarly, SMD haplotype determination applied to genetic mapping could increase the resolution of linkage analysis and facilitate crossover detection. While other approaches applicable to haplotype determination have amplified DNA from microdissected

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chromosomes (27) or spermatocytes (28), ours offers distinctive advantages. Direct haplotype determination with SMD and booster PCR not only obviates the need for pedigrees but is also technically simple and applies to DNA samples from either sex.”

6. Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kostrikis et al. (Science, vol. 279, pp. 1228-1229, 1998; cited in the IDS and in the previous office action) and Ruano et al. (PNAS USA, vol. 87, pp. 6296-6300, 1990; cited in the IDS) as applied to claim 2 above, and further in view of Kinjo et al. (Nucl. Acids Res., vol. 23, pp. 1795-1799, 1995; cited in the IDS).

A) Regarding claims 6 and 7, Kostrikis et al. teach detection of labeled nucleic acid segments in small volumes, but do not teach detection using confocal microscope and fluorescence detection in individual drops.

B) Kinjo et al. teach detection of hybridization of oligonucleotides to a single DNA molecule using fluorescence correlation spectroscopy to detect single molecules (Abstract; page 1795, first paragraph; Fig. 1; page 1796, second and third paragraphs).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the fluorescence correlation spectroscopy of Kinjo et al. in the detection of single molecules in the method of haplotyping of Kostrikis et al. and Ruano et al. The motivation to do so, provided by Kinjo et al., would have been, as stated by Kinjo et al. (page 1799, first paragraph):

“Due to the high sensitivity and small volumes used, very small amounts of material (fmol) are needed. Since FCS can be used to detect single molecules, we foresee this method will be able to identify specific RNA and DNA sequences in solution, as well as in the cellular environment.”

7. No claims are allowed.

***Conclusion***

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka  
Primary Examiner  
Art Unit 1637

*Teresa Strzelecka*

*9/19/07*